myelitis [2]. In the aforementioned review, Spellberg and Lipsky suggested that chronic osteomyelitis can be effectively treated based on the antibiotic susceptibility of the pathogen(s) and pharmacokinetics with oral antibiotics as well as parenteral therapy. They concluded that oral antibiotic therapy with the proper agent was an effective alternative to parenteral antibiotics [11].

Conclusion

While the studies to date do not provide a clear optimal antibiotic choice, duration or route of administration for the treatment of chronic osteomyelitis, some observations are consistent from the data available. First, knowing the pathogen, pathogen sensitivities, antibiotic bone penetration and antibiotic toxicities do help the treating physician make the best choice for a specific patient and clinical scenario. It is important, whenever possible, to establish a microbiological diagnosis (or at least to obtain adequate bone tissue for culture in the lab) prior to initiating antibiotics. As the current recommendation for duration of therapy is typically 4-12 weeks, antibiotic exposure and toxicity can be significant. Second, in certain situations, oral therapy is just as effective as parenteral therapy and there are more studies supporting oral therapy than parenteral therapy. There is sufficient data to support the use of an active oral fluoroquinolone for osteomyelitis caused by gram-negative organisms, the use of an active fluoroquinolone with rifampin for *S. aureus* osteomyelitis, and the consideration of using trimethoprim-sulfa with rifampin for *S. aureus* osteomyelitis if both agents are active. Using an active fluoroquinolone alone for *S. aureus* osteomyelitis should be avoided due to the development of resistance while on monotherapy and the higher rate of relapse after therapy is completed. Third, adding rifampin to a variety of antibiotics seems to improve cure rates when coupled with another known active agent when treating *S. aureus* osteomyelitis. Fourth, surgical debridement and removal of infected hardware, when possible, generally improves treatment outcomes. Fifth, oral clindamycin which is routinely used for the treatment of acute *S. aureus* osteomyelitis in children [17–20], has not been well studied for the treatment of chronic osteomyelitis in adults. Finally, it is also important to keep in mind that antibiotics are only effective when they reach the site of infection. Adequate vascularized soft tissue coverage of infected bone, debridement of any significant necrotic tissue and sequestrum, and adequacy of blood flow to the affected site are likely critical factors in improving outcomes.

Clearly, additional RCTs are needed to answer the question regarding the optimal agent, route and duration of therapy for treating chronic osteomyelitis in adults.

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QUESTION 6: What is the recommended suppressive antibiotic therapy for the treatment of chronic osteomyelitis after fracture fixation when the implant cannot be removed?

RECOMMENDATION: Suppressive therapy with culture-specific antibiotics is aimed at allowing fracture healing prior to implant removal and definitive infection management.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Infection after surgical treatment of fractures is a complication with significant morbidity, and in rare cases even mortality. Infections have often been classified according to the time interval between surgery and occurrence, although the distinction between acute and chronic infections has recently been challenged. Early infections are mainly caused by virulent microorganisms, such as *Staphylococcus aureus*, and diagnosed within the first three weeks of surgery. Delayed infections are typically due to less virulent bacteria, such as coagulase-negative Staphylococci, and develop between 3 and 10 weeks. Finally, late infections, occur after 10 weeks and are either caused by haematogenous seeding or by recurrence of inadequately-treated early infection [1]. Infections that occur following open reduction internal fixation (ORIF) are typically caused by biofilm-forming bacteria, which adhere to the implants [2]. In approximately one week, a mature biofilm already forming, which makes it less likely to for antibiotics alone to eradicate bacteria [3].

Common treatment for implant-related infection obeys to three established principles: surgical debridement, antibiotic therapy and eventual implant removal or staged exchange. However, in ORIF and with fracture-related infection (FRI), implant removal is unsuitable because of resulting fracture instability that often leads to prolonged infection [4,5]. This has consequences for the other aspects of treatment – if the implant is retained, the biofilm remains. Surgical debridement can remove the bulk of the bacterial load, but adjuvant antibiotic therapy must be directed towards the biofilm present. If the implants are retained, treatment consists of thorough surgical debridement, tissue cultures and long-term antibiotic suppressive therapy with rifampin-based combination antibiotic therapy. To date, only two classes of drugs have shown the properties that are needed for control of biofilm forming bacteria. Rifampin and other rifamycins act on biofilm active Staphylococci [6–11] and fluoroquinolones on gram-negative bacilli [12,13].

In the event of retained hardware after debridement of an acute infection following ORIF, the recommended antibiotic combination therapy should start immediately after the first surgical intervention and consists of 10 days of intravenous (IV) vancomycin and rifampin. Vancomycin was the agent of choice for empirical therapy because of its activity against a broad spectrum of microorganisms, the high incidence of gram-positive infections and the synergetic effect with rifampin [14–16]. Vancomycin therapy was started twice daily (1,000 mg IV), and was adjusted to maintain serum levels between 15 and 20 mcg/ml. Rifampin was given twice daily (450 mg IV). After tissue cultures identify the responsible bacterial pathogens and susceptibility data becomes available, vancomycin therapy can be switched to another, narrow spectrum antibiotic as indicated. Rifampin is continued unless rifampin-resistant bacteria are found.

Zimmerli et al. [2,6] assessed the effectiveness of this protocol in a randomized controlled trial, and after the IV administration period, oral combination antibiotic therapy with rifampin was continued for ten additional weeks. They reported 100% success in cases where both antibiotics were administered compared to 58% success when only ciprofloxacin was received. Barberan et al. [17] and Drancourt et al. [18] also studied infection following ORIF and evaluatied the effect of antibiotic combination therapy with rifampin reporting good results. Drancourt et al. [18] analyzed both periprosthetic joint infection (PJI) and FRI treated with initial retention and combination antibiotic therapy, and reported a success rate of 48% after an average follow-up of 23.5 months. The study of Barberan et al. [17] only included patients with infections following ORIF and demonstrated a success rate of 72%. In a prospective observational cohort study, Tschudin-Sutter et al. [19] analyzed 233 patients with orthopaedic implant-related infections of which 52.4% (122/233) were infections related to ORIF, for which the success rate was 90.2% (110/122) with the use of rifampin-combination regimen as suppressive therapy. This was seen on patients with implant retention after two years of followup. Patients were identified for inclusion using strict selection criteria (the duration of clinical symptoms was no longer than three weeks): stable implant, intact soft tissues, no abscess or sinus tract and the causative pathogen was susceptible to antibiotics with activity against surface-adhering microorganisms (i.e., rifampin for *S. aureus* or coagulase-negative Staphylococci and ciprofloxacin for gram-negative pathogens) [19]. This is so far the largest study evaluating patients with implant-associated infection managed with retention and long-term suppressive antibiotic therapy.

It is important to highlight the critical aspect of implant stability, as loose implants cannot be retained even if infection becomes evident at very early stages. Worlock et al. [4] demonstrated in a rabbit model that unstable tibial fractures were associated with significantly higher rates of osteomyelitis than those which were stable. These implants can often be retained when an acute infection develops after fracture fixation. Implant removal is generally undesirable in cases of acute infection as ORIF serves two different goals. First, the stability achieved by fixation is critical for fracture healing. When conditions are created in which micromotion between bone fragments is possible, resorption and necrosis of the affected bone will occur [5]. Second, the aim of operative fracture management and early mobilization is to prevent loss of function due to scarring of the surrounding soft tissue or joint stiffness. Special consideration should be given to infections after intramedullary fixation, with the popular belief that eradication of the infection is not feasible without implant exchange [20]. Chen et al. [21] reported on 23 infections following intramedullary (IM) nailing of the femur for fractures. The patients were divided into two groups where one group with IM nails had their nails removed and an external fixator was placed. All femur fractures with retained IM nails healed (12/12) and were infection free at followup of average 25 months. Only 7 of 11 patients (64%) in the external fixator group healed. Whereas removal or exchange of the implant provides the opportunity to remove the biofilm and thus reduce the bacterial load, in cases of implant retention the surgical debridement and adjuvant antibiotic therapy play a more important role.

In conclusion, in the situation of FRI where debridement and implant retention is chosen as the treatment strategy, rifampin (rifamycins) can be an effective adjuvant agent in suppressing gram-positive organisms while ciprofloxacin (fluoroquinolones) can be effective in suppressing gram-negative organisms.

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QUESTION 7: Is there a role for hyperbaric oxygen therapy (HBOT) and other non-antibiotic methods for the treatment of chronic osteomyelitis/implant infections?

RECOMMENDATION: There is limited evidence for the efficacy of hyperbaric oxygen (HBO) in the treatment of post-traumatic bone infections.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 86%, Disagree: 5%, Abstain: 9% (Super Majority, Strong Consensus)

RATIONALE

HBOT has been proposed as an adjunctive therapy in the management of refractory osteomyelitis, which was defined as chronic osteomyelitis that persists or recurs after appropriate interventions have been performed or where acute osteomyelitis has not responded to accepted management techniques [1]. The procedure involves the intermittent inhalation of 100% oxygen in chambers pressurized above one atmosphere absolute (typically to about 2 to 2.5 atmosphere absolute (ATA)). It is based on the premise that increased tissue oxygen levels will enhance healing. Although adverse events are typically self-limiting, more serious potential complications include baro-traumatic otitis, pneumothorax, myopia and seizures [2].

While initially there was some enthusiasm about the use of HBOT in refractory osteomyelitis, this appears to have waned with only one case series published since 2004 [3]. Prior to this, a small number of descriptive studies were published that reported encouraging results [4,5]. A systematic review by Goldman in 2009 examined the evidence for HBOT in wound healing and limb salvage. Five studies were classified as "moderate" strength evidence (the remaining 10 being either "low" or "very low") [6]. In the first of these Morrey et al., reported on the outcomes of HBOT in 40 patients who had recurrent infection for more than 6 months after at least 1 surgical procedure [7]. Following surgery, antibiotics and HBOT, 85% of patients were reported to be disease-free at one year.

Davis et al. performed a retrospective study on 38 patients with actively draining wounds and at least 1 failed previous surgical procedure [8]. Complete healing was achieved, again in combination with surgery and antibiotics, in 89% of cases. From 1998 to 2004 Chen et al., published three overlapping case series involving patients who presented with recurrence of infection following prior surgical treatment [9–11]. The success rate of standard treatment, involving aggressive debridement, antibiotics and HBOT, was reported as 79% to 92% (note that the 2003 study was not included in the Goldstein systematic review). The findings from all of these non-comparative studies are however difficult to interpret and confounded by the fact that HBO was used as part of a multi-modal treatment strategy. Furthermore, it is not clear if the initial failed surgical procedures were performed by experienced musculoskeletal infection surgeons. There was only one comparative study included in the Goldman systematic review. Esterhai et al. performed a prospective non-randomized controlled trial and found that HBOT had no effect on length of hospitalization, initial clinical outcome or the late recurrence of infection [12]. The only clinical study published since the systematic review in 2009, described the experience of a single center with HBOT in general and did not provide a detailed description specific to the chronic refractory osteomyelitis patients [3].

Recently, the effect of HBOT on implant-associated infection was further drawn into question. Büren et al. illustrated in a standardized murine model that HBOT did not have a beneficial effect on the local infection or the immune response to the infection compared to standard therapy alone [13]. Interestingly, they also noted delayed bone healing and a higher rate of non-unions at 28 days in the HBOT group. Ultimately, there is currently only limited evidence